EURORDIS
THERAPEUTIC REPORT
September 2021
ISSUE 8
UPDATE ON THERAPEUTIC DEVELOPMENT AND PATIENT INVOLVEMENT IN EMA ACTIVITIES

GENERAL NEWS

EURORDIS Summer School 2022

The *EURORDIS Summer School* provides rare disease patient advocates and researchers working with rare diseases with the knowledge and skills needed to become experts in medicines research and development.

The *next training of the EURORDIS Summer School on Medicines Research & Development will take place from 6-10 June 2022 in Barcelona*. Topics covered include clinical trials methodology, clinical research, ethics in medicines development, regulatory affairs, and marketing authorisation.

Deadline for applications 15 November, and the outcomes will be out by the end of January. *Apply here*!
For more information contact *tamara.kovazh@eurordis.org*

IN THIS ISSUE

EURORDIS calls for additional doses of COVID-19 vaccine

EURORDIS-Rare Diseases Europe and the rare diseases community are calling on national policy makers to consider booster doses for people whose immune systems have not fully responded to the initial vaccination, including people living with a rare disease, and additional measures to encourage more citizens to get vaccinated against COVID19.

People with moderate or severe primary immunodeficiency, including many transplant recipients, dialysis patients, people living with cancer and some rare diseases, may not build the same level of immunity to the two-dose vaccines compared to those who are not immunocompromised. In this regard, it is crucial that a third or even a fourth dose of the COVID-19 vaccine, when appropriate, be regarded by all national authorities across Europe as an extension of the primary vaccination course for people with weakened immune systems. Even though some countries have already put such a system in place, EURORDIS expresses concerns that too few benefited from this measure.

Consideration for an additional dose of the COVID-19 vaccine should also be given to carers and health care providers in direct contact with people with moderate or severe immune conditions. For patients who remain vulnerable to the virus after the third or fourth doses, EURORDIS urges health authorities to consider the administration of monoclonal antibodies as pre-exposure or post-exposure prophylaxis, as has already been decided in some countries on a compassionate basis, pending the final evaluation of evidence. This, however, should not affect EU countries' commitment to donate 200 million doses of vaccines to COVAX and AVAT.
For more information, please *read the press release here*!

What is the Patient Engagement Open Forum?

Patient Engagement Open Forum (PEOF) is a series of virtual events where all the actors work together, in a multi-stakeholder context, to turn patient engagement into reality. The PEOF is jointly organised by PFMD, EUPATI and EPF and is one of the main outcomes of the Innovative Medicines Initiative (IMI)-funded *PARADIGM* (**Patients Active in Research and Dialogues for an Improved Generation of Medicines)** project.

IMI-PARADIGM was a public-private partnership led by the European Patients' Forum (EPF) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) which aimed for better patient engagement in medicines development and finished in 2020. EURORDIS played a major role in the governance of the project and co-led the work package on developing a roadmap ensuring patient engagement sustainability in the long run which led to the following publication *'Sustaining Meaningful Patient Engagement Across the Lifecycle of Medicines: A Roadmap for Action'*.

Another main outcome was the *PARADIGM PE toolbox* which centralises co-created recommendations, tools and relevant background information to make PE in medicines development easier for all.

Adapted from the IMI PARADIGM website. Check the tools here!

PEOF October 2021

The Patient Engagement Open Forum 2021 is organized online as a series of events, once every quarter. The events span over two afternoons (CET), back-to-back, four times a year: April, June, October, and December.

The last one took place online, 6 & 7th October. The first day, was focused on the patient pathway in precision medicine and electronic medicines leaflets. The second day was on PE in the Medtech Sector and harmonized Global Principles for Remunerating the Patient Community for interactions with the pharmaceutical industry.

This last item, the Global Principles were co-created with a Steering Committee of representatives from the patient community and the pharmaceutical industry by harmonizing and building on previous collaborative work to ensure key values govern the remuneration process: transparency, fairness, equity, and ethics. These principles are now under Public Consultation and will run until November 1st, 2021. Although the survey takes 40 minutes, remuneration continues to be an obstacle in driving forward transparent and ethical patient engagement between the industry and the patient community. Your opinions and views matter, answer now here!

For more information on the different sessions, please see the slides and recordings here.

Pharmacovigilance Risk Assessment Committee (PRAC) September 2021

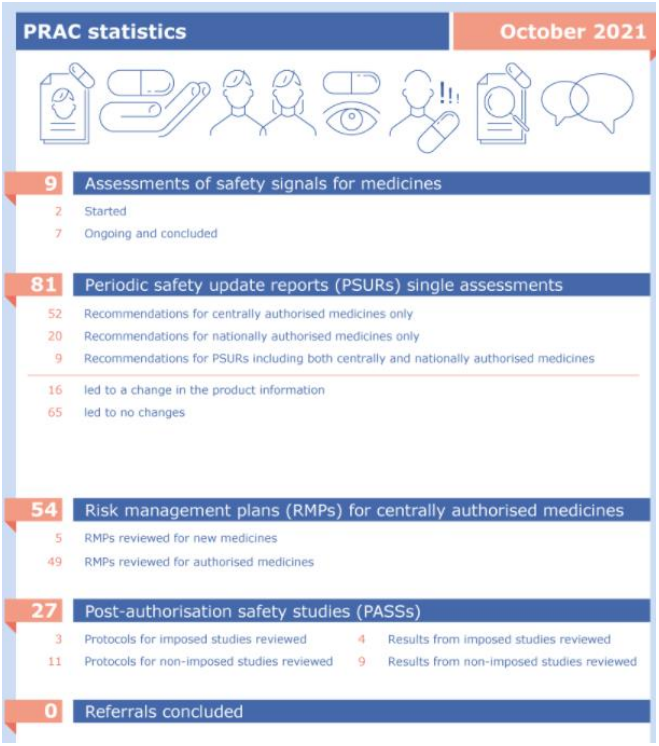
Minutes January 2021
Agenda September 2021
Meeting Highlights Sept 2021

EMA review of meningioma risk with nomegestrol & chlormadinone medicines

EMA has started a review of medicines containing the active substance nomegestrol or chlormadinone. These medicines can be used, alone or in combination with other active substances, to treat gynaecological disorders such as amenorrhea (absence of menstrual periods) and other menstrual disorders, uterine bleeding, endometriosis (a condition in which tissue similar to the lining of the womb grows elsewhere in the body), breast tenderness, as hormone replacement therapy or as contraceptives (birth control).

The review was requested by the French medicines agency (ANSM) following new data from two epidemiological studies carried out in France in women taking these medicines to investigate the risk of meningioma, a tumour of the membranes covering the brain and spinal cord. This tumour is usually non-malignant and is not considered to be a cancer, but due to their location in and around the brain and spinal cord, meningiomas can in rare cases cause serious problems.

EMA's safety committee (PRAC) will now examine the available evidence and make recommendations.
For more information, please see *EMA website*.



Medicines safety resources

- List of medicines under additional monitoring
- EudraVigilance
- Shortages catalogue
- Recommendations on medication errors
- Good Pharmacovigilance Practices
- Patient registries
- Rules of procedure on the organisation and conduct of public hearings at the PRAC

Click on the image to get the latest issue of *QPP Update*, an EMA newsletter with the latest news on EU Pharmacovigilance

Orphan medicines key figures

Since 2000

2428 Orphan designations

243 Orphan designations included in authorised indication

210 Authorised OMPs

84 To be used in children

6 Removed from the market

69 Marketed, but no longer "orphans"

To date

135

Products with a marketing authorisation and an orphan status in the European Union

20 October 2021

CHMP Meeting Highlights September 2021

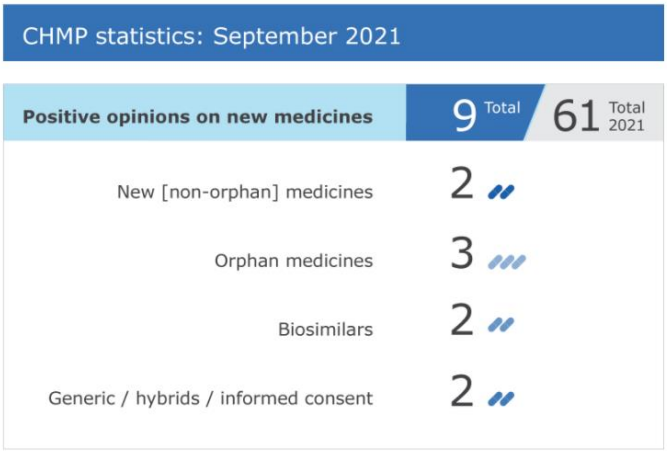
Minutes June 2021
Agenda September 2021
Meeting Highlights Sept 2021

In September, the CHMP recommended **9 medicines for approval, 3 orphan medicines**:

- *Artesunate Amivas* (*artesunate*), for the initial treatment of severe malaria in adults and children. This medicine has an orphan designation because malaria has a low prevalence in the European Union.
- *Brukinsa* (*zanubrutinib*), for the treatment of Waldenström's macroglobulinaemia.
- *Qinlock* (*ripretinib*) for the treatment of advanced gastrointestinal stromal tumour (GIST).
- Conditional marketing authorisation for *Gavreto (pralsetinib)* for the treatment of non-small cell lung cancer.
- *Vumerity (diroximel fumarate)* for the treatment of adult patients with relapsing remitting multiple sclerosis.
- Two biosimilars, *Hukyndra and Libmyris (both containing adalimumab) for* the treatment of inflammatory auto-immune disorders such as arthritis psoriasis, inflammatory bowel disease or uveitis. *A biosimilar medicine is a biological medicine that is highly similar to another biological medicine that is already authorised for use.*

The CHMP also recommended **9 extensions of therapeutic indication,** and recommended granting marketing authorisations for two generic medicines.

For further details, read the full *CHMP meeting highlights*.



Click on the image to get the latest issue of ***Human Medicines Highlights***, a newsletter published by EMA address to organisations representing patients, consumers and healthcare professionals summarising key information on medicines for human use.

Minutes July 2021
Agenda September 2021
Meeting Report September

COMP September 2021 meeting update

During the September plenary, the COMP adopted **17 positive opinions** on the designation of medicines as orphan medicinal products to the European Commission (EC). For further information, please see the *meeting report.*

Please find below the list of indications covered in the medicines that were recommended for orphan designation:

- Megalencephalic leukoencephalopathy with subcortical cysts, Consorcio Centro de Investigación Biomédica en Red, M.P.;
- Burkitt's lymphoma, IQVIA RDS Ireland Limited;
- Tuberous sclerosis, Marinus Pharmaceuticals Emerald Limited;
- Frontotemporal dementia, Pharma Gateway AB.
- Cone-rod dystrophy, Variant;
- Krabbe disease, Diamond Pharma Services Ireland Limited;
- Mucopolysaccharidosis type I, TMC Pharma (EU) Limited;
- Bronchopulmonary dysplasia, Exo Biologics;
- Osteopetrosis, Fondazione Telethon;
- Ovarian cancer, Kinesys Consulting NL B.V.;
- Hypoparathyroidism, Voisin Consulting Life Sciences;
- Diffuse large B-cell lymphoma, Roche Registration GmbH;
- Small cell lung cancer, AbbVie Deutschland GmbH & Co. KG;
- Mucopolysaccharidosis type II (Hunter's syndrome), Parexel International (Irl) Limited;
- Haematopoietic stem cell transplantation, Priothera;
- Fragile X syndrome, Comac Medical Ltd.;
- Glioma, Karyopharm Europe GmbH.

Summaries of positive opinions on orphan designations are available on the *EMA website*.

Medicinal Product	Marketing Authorisation Holder	Therapeutic Indication	Date of Marketing Authorisation
Elzonris® (tagraxofusp)	Stemline Therapeutics B.V.	Adults with blastic plasmacytoid dendritic cell neoplasm (BPDCN)	07/01/2021
Inrebic® (fedratinib)	Celgene Europe BV	Adults with myelofibrosis (a rare form of blood cancer)	08/02/2021
Lumoxiti® (moxetumomab pasudotox) *(Withdrawn by the company)*	AstraZeneca AB	Adults with hairy cell leukaemia, a cancer of the white blood cells	08/02/2021
Evrysdi® (risdiplam)	Roche Registration GmbH	5q spinal muscular atrophy (SMA) in patients +2 months of age with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies	26/03/2021
Pemazyre® (pemigatinib)	Incyte Biosciences Distribution B.V.	Adults with cholangiocarcinoma	26/03/2021
Sogroya® (somapacitan)	Novo Nordisk A/S	Growth hormone deficiency	31/03/2021
Koselugo® (selumetinib)	AstraZeneca AB	Neurofibromatosis type 1	17/06/2021
Enspryng® (satralizumab)	Roche Registration GmbH	Neuromyelitis Optica Spectrum disorders (NMOSD)	24/06/2021
Bylvay® (odevixibat)	Albireo	+6 months with progressive familial intrahepatic cholestasis (PFIC)	16/07/2021
Skysona® (elivaldogene autotemcel)	bluebird bio (Netherlands) B.V.	Under 18 years of age with early cerebral adrenoleukodystrophy (CALD)	16/07/2021
Imcivree® (setmelanotide)	Rhythm Pharmaceuticals Limited	+6 years who have pro-opiomelanocortin (POMC) deficiency or leptin receptor (LEPR) deficiency	16/07/2021
Abecma® (idecabtagene vicleucel)	Celgene Europe BV	Adults with multiple myeloma (a cancer of the bone marrow)	18/08/2021
Voxzogo® (vosoritide)	BioMarin International Limited	Achondroplasia in patients aged +2 years	26/08/2021
Minjuvi® (tafasitamab)	Incyte Biosciences Distribution B.V.	Adults with diffuse large B-cell lymphoma (DLBCL)	26/08/2021

Please click also on the following links to see:

Orphan medicinal products authorised during 2021

Orphan medicinal products authorised since 2000

PDCO June to September meetings to be updated when EMA publishes the information

Minutes April 2021
Agenda May 2021
Meeting Report May 2021

PDCO May 2021 meeting update

In May, the PDCO adopted **12 positive opinions** agreeing *paediatric investigation plans (PIPs)* for the medicines below. The PIP aims to generate the necessary quality, safety and efficacy data through studies to support the authorisation of the medicine for use in children of all ages.

- Macitentan, from Janssen-Cilag International N.V., for the treatment of functional single ventricle heart disease with total cavo-pulmonary connection;
- Finerenone, from Bayer AG, for the treatment of heart failure;
- Ralinepag, from United Therapeutics Corporation, for the treatment of pulmonary arterial hypertension;
- Allogeneic skin-derived ABCB5-positive mesenchymal stem cells, from RHEACELL GmbH & Co. KG, for the treatment of epidermolysis bullosa;
- Adeno-associated viral vector serotype 8 containing the human glucose-6-phosphatase gene (DTX401), from Ultragenyx Germany GmbH, for the treatment of glycogen storage disease type Ia;
- Maralixibat Chloride, from Mirum Pharmaceuticals Inc., for the treatment of biliary atresia;
- Odevixibat, from Albireo AB, for the treatment of Alagille syndrome;
- Recombinant monoclonal antibody to sialic acid-binding Ig-like lectin 8, from Allakos Inc, for the treatment of eosinophilic gastrointestinal inflammatory disorders;
- Cilgavimab (AZD1061), from AstraZeneca AB, for the prevention or treatment of COVID-19;
- Tixagevimab (AZD8895), from AstraZeneca AB for the prevention or treatment of COVID-19;
- Pralsetinib, from Roche Registration GmbH, for the treatment of thyroid neoplasms;
- Autologous selected renal cells, from ProKidney, for the treatment of chronic kidney disease;

The PDCO also adopted opinions on **product-specific waivers, modifications to an agreed PIP and compliance check** that can be consulted in the *meeting report.*

For further information on the work of the PDCO for this 2021, please see the *work plan.*

For a comprehensive list of opinions and decisions on PIPs, please check the *EMA website*.

Minutes May 2021
Agenda September 2021
Meeting Report Sept 2021

CAT September 2021 meeting update

In September the Committee for Advanced Therapies (CAT) finalised **8 scientific recommendations on the classification of advanced therapy medicinal products** (ATMPs) depicted below.

The outcome of these assessments can be found here: *Summaries of scientific recommendations on classification of ATMPs*.

The following products were classified as **gene therapy medicinal products:**

- Recombinant serotype 9 adeno-associated virus encoding a codon-optimised human galactosylceramidase transgene, intended for the treatment of Krabbe disease;
- HEK293 cells transfected with a lentiviral vector to express Wilms' tumour antigen (WT1) and the antigen presenting molecule, cluster of differentiation 1d, intended for the treatment of WT1-expressing tumours.

The following products were classified as somatic cell therapy medicinal products:

- Autologous population of selected renal cells, intended for the treatment of chronic kidney disease;
- Allogeneic natural killer cells armed with anti-CD20 monoclonal antibody, intended for the treatment of B-Cell Non-Hodgkin lymphoma.

The following product was classified as **advanced therapy medicinal product**:

- Autologous adipose mesenchymal stem cells, intended for cartilage defects of degenerative origin and for the treatment of osteoarthritis;
- Wharton's jelly derived mesenchymal stem cells, intended for the treatment of:
    - rheumatoid arthritis;
    - systemic lupus erythematosus;
    - systemic sclerosis.

The following products **do not fulfil the definition of an advanced therapy medicinal product**:

- Minimally manipulated autologous pancreatic islets, intended for the treatment of chronic pancreatitis and recurrent acute pancreatitis immediately following pancreatectomy;
- Ribonucleoprotein (RNP), a complex of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) Cas 9 and sgRNA, delivered by a novel synthetic non-viral vector, for the excision of exon 80 of the human COL7A1 gene, intended for the treatment of recessive dystrophic epidermolysis bullosa.

For more information, see also the *EMA meeting report.*

PATIENTS' AND CONSUMERS' WORKING PARTY

The Patients' and Consumers' Working Party (PCWP), established in 2006, serves as a platform for exchange of information and discussion of issues of common interest between EMA and patients and consumers. It provides recommendations to EMA and its human scientific committees on all matters of interest in relation to medicines.

For more information, see also the *PCWP mandate, objectives and rules of procedure.*

EMA PCWP and HCPWP June meeting

Last 21st and 22nd September took place a *2 days virtual meeting* which brought together all eligible patient and consumer and healthcare professionals organisations and members of the Patients' and Consumers' Working Party (PCWP) and Healthcare Professionals' Working Party (HCPWP).

During the first day of meeting, the Agency introduced the latest updates on COVID-19. EMA also presented on ongoing activities related with the impact of pharmacovigilance activities on healthcare and patient safety. An update on the implementation of the Clinical Trials regulation was also provided.

On the second day, the PCWP/HCPWP discussion focused on communication and stakeholder engagement topics linked with EMA's future extended mandate and Big Data. The final part of the meeting was dedicated to topic prioritisation for 2022, key dates and activities.

For more information, please see the *agenda, the presentations* and the *summary of the meeting here*.

EMA Glossaries

The EMA just published a *medical terms simplifier* that gives plain-language descriptions of medical terms commonly used in information about medicines.

A *glossary of regulatory terms* that gives definitions for the main terms used on the EMA website and in their documents has also been published.

For more information, please check the *glossaries here.*

GLOSSARY

Accelerated assessment
Rapid assessment of medicines in the centralised procedure aimed at facilitating patient access to new medicines that address an unmet medical need. Accelerated assessment usually takes 150 evaluation days, rather than 210.

Advanced therapies or advanced-therapy medicinal products (ATMPs)
ATMPs are new medical products based on genes, cells and tissues, which offer new treatment opportunities for many diseases and injuries. There are four main groups:

Gene-therapy medicines
They are medicines that contain genes leading to a therapeutic effect. They work by inserting 'recombinant' genes into cells, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources.

Somatic-cell therapy medicines
These contain cells or tissues that have been manipulated to change their biological characteristics. They can be used to cure, diagnose or prevent diseases;

Tissue-engineered medicines
These contain cells or tissues that have been modified so they can be used to repair, regenerate or replace tissue.

Combined advanced-therapy medicines
These are medicines that contain one or more medical devices as an integral part of the medicine. An example of this is cells embedded in a biodegradable matrix or scaffold.

Authorisation under exceptional circumstances
It allows patients access to medicines that cannot be approved under a standard authorisation as comprehensive data cannot be obtained, either because there are only very few patients with the disease, the collection of complete information on the efficacy and safety of the medicine would be unethical, or there are gaps in the scientific knowledge. These medicines are subject to specific post-authorisation obligations and monitoring.

Compliance check
It is performed to verify that all the measures agreed in a *Paediatric Investigation Plan* (PIP) and reflected in the Agency's decision have been conducted in accordance with the decision, including the agreed timelines. Full compliance with all studies/measured contained in the PIP is one of several prerequisites for obtaining the rewards and incentives provided for in Articles 36 to 38 of the Paediatric Regulation.

Conditional marketing authorisation
It is granted to a medicine that addresses unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

Designation, orphan medicinal product
A status assigned to a medicine intended for use against a rare condition. The medicine must fulfil certain criteria for designation as an orphan medicine so that it can benefit from incentives such as protection from competition once on the market.

European Public Assessment Report (EPAR)
It is a lay-language document, which provides a summary of the grounds on which the EMA/CHMP based its recommendation for the medicine to receive a marketing authorisation. This happens when a manufacturer develops a generic medicine based on a reference medicine, but with a different strength or given by a different route.

Hybrid application for marketing authorisation
Hybrid applications rely partly on the results of tests on the reference medicine and partly on new data from clinical trials.

Informed consent application for marketing authorisation
An informed consent application makes use of data from the dossier of a previously authorised medicine, with the marketing authorisation holder of that medicine giving consent for the use of their data in the application.

Orphan Legislation
Regulation (EC) No 141/2000 on orphan medicinal products

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GLOSSARY

Paediatric Investigation Plan (PIP)
It sets out a programme for the development of a medicine in the paediatric population. It aims to generate the necessary quality, safety and efficacy data through studies to support the authorisation of the medicine for use in children of all ages. These data have to be submitted to the EMA, or national competent authorities, as part of an application for a marketing authorisation for a new medicine, or for one covered by a patent.

Paediatric Use Marketing Authorisation (PUMA)
It is a dedicated marketing authorisation for medicinal products indicated exclusively for use in the paediatric population, or subsets thereof, with, if necessary, an age-appropriate formulation. It has been designed to promote paediatric development of already authorised products which are no longer covered by a patent. Benefits are 8 years of data protection and 10 years market protection

Patient-reported outcomes (PROs)
Measurements based on data provided directly by patients regarding their health condition without interpretation of the patient's response by a clinician or anyone else.

Patient-reported outcome measures (PROMs)
They are instruments, scales, or single-item measures that have been developed to measure PROs, for example a self-completed questionnaire to assess pain.

Periodic Safety Update Reports (PSURs)
Periodic reports that the evaluate the benefit-risk balance of a medicine as evidence is gathered in clinical use. They are submitted by marketing authorisation holders at defined time points after the authorisation.

Post-authorisation efficacy studies (PAES)
PAES are studies relating to authorised medicinal products conducted within the therapeutic indication with the aim of addressing well-reasoned scientific uncertainties on aspects of the evidence of benefits of a medicine that could not be resolved before authorisation or were identified afterwards.

Post-authorisation safety studies (PASS)
A PASS is carried out after a medicine has been authorised to obtain further information on its safety, or to measure the effectiveness of risk-management measures. The PRAC is responsible for assessing the protocols of imposed PASSs and for assessing their results.

Prevalence
In the context of the Orphan Legislation, the prevalence refers to the number of persons with the condition at the time the application is made, divided by the population of the European Union (EU) at that time. It requires demonstration through authoritative references that the disease or condition for which the medicinal product is intended affects not more than 5 in 10,000 persons in the EU, when the application is made.

Public summaries of PDCO evaluations of PIPs
They describe the applicant's proposal for the development of their medicine in children, the PDCO's conclusion on the potential use of the medicine in the paediatric population, the plan agreed between the committee and the applicant at the completion of the procedure (including any partial waivers or deferrals) and the next steps.

Referral procedures for safety reasons
A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or a class of medicines on behalf of the European Commission or a Member State.

Risk Management Plans (RMPs)
RMPs are regulatory documents submitted by medicine developers when they apply for marketing authorisation and include information on the medicine's safety profile; how its risks will be prevented or minimised in patients; plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine; risk factors for developing adverse reactions; measuring the effectiveness of risk-minimisation measures.

Scientific advice/protocol assistance
Through scientific advice, companies can ask the EMA for advice on whether they are conducting the appropriate tests and studies during the clinical development of a given product. In the case of orphan medicines for the treatment of rare diseases, it also includes advice on1) the demonstration of significant benefit for the designated orphan indication and on 2) similarity or clinical superiority over other medicines; which are criteria for the authorisation of an orphan medicine.

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Significant benefit

Demonstrating a significant benefit, this is demonstrating a "clinically relevant advantage or a major contribution to patients" is one of the criteria that medicines for the treatment of rare diseases must fulfil to benefit from 10 years of market exclusivity once they have been authorised. For further information, read the *workshop report: Demonstrating significant benefit of orphan medicines*, held at the EMA in December 2015.

Safety signal

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature, but their presence does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of a safety signal is required to establish whether or not there is a causal relationship between the medicine and the adverse event.

Similar active substance

It means an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of them) and which acts via the same mechanism.

Scientific Advisory Group (SAG)

SAGs have been established to provide an independent recommendation on scientific/technical matters related to products under evaluation through centralised regulatory procedures and referrals by the CHMP or any other scientific issue relevant to the work of the Committee.

Waiver

A waiver can be issued if there is evidence that the medicine concerned is likely to be ineffective or unsafe in the paediatric population, or that the disease or condition targeted occurs only in adult populations, or that the medicine, or the performance of trials, does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

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